Which processes drive the accumulation of cytotoxic CD8+ T cells in the lungs of COPD patients?

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Ethical review	Approved WMO
Status	Pending
Health condition type	Bronchial disorders (excl neoplasms)
Study type	Observational invasive

Summary

ID

NL-OMON31140

Source
ToetsingOnline

Brief title
CD8+ T cell and COPD

Condition

- Bronchial disorders (excl neoplasms)

Synonym
chronic obstructive pulmonary disease (COPD)

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Astma Fonds

Intervention

Keyword: CD8+ T cell, COPD

Outcome measures

Primary outcome

The initial studies using the paired T cells from lung and circulation will focus on three items:

1 Assessment of replicative history

2 Comparison of the clonal composition

3 Determination of the lung T cell transcriptosome

From these analyses we will select key markers that are typically expressed by lung residing T cells, to look for differences between participant subgroups, particularly those with and without established COPD. Depending on the characteristics of the specific markers we will use immunohistochemistry on the tissue blocks, FACS analysis of T cells and RT PCR where appropriate. FACS analyses will be performed on total CD8+ T cells and T cells specific for respiratory viruses

Secondary outcome

We aim to obtain BAL CD8+ T cells from the lobe that will be removed during the operation by bronchoscopy and compare these cells to those isolated from the tissue.

Study description

Background summary

Since increased numbers of CD8+ T cells have been found in various tissue compartments in COPD lungs, it has been hypothesized that these cells are implicated in the pathogenesis of COPD. However, it is far from established whether, and if yes how, these cells contribute to the development of COPD in smokers. Increased insight into these mechanisms may come from knowledge of the processes that drive the accumulation of CD8+ T cells in lung tissue.
From studies on the cell surface phenotype of CD8+ T cells in various phases of viral infections much has been learned about the biology of these cells that, however, generally were isolated from the circulation. We recently started to study CD8+ T cells isolated from human lung tissue. It became clear that lung residing CD8+ T cells have quite a different phenotype than their peripheral blood counterparts. Specifically, the main findings from our initial study were (1) the local accumulation of resting but differentiated CD8+ T-lymphocytes specific for cleared respiratory viruses, (2) the presence of high numbers activated CD4+ and CD8+ T cells of yet undetermined specificity in the lung and (3) the low activation threshold of lung residing T cells. In addition, our findings from a recently finished NAF project support a role for Granzyme B and Granzyme B+ CD8+ T-lymphocytes in the development towards COPD in cigarette smokers. Altogether, however, these data leave a number of relevant questions open, especially in relation to the mechanisms regulating the homeostasis of lung residing CD8+ T cells.

Study objective

In the present project we aim to characterize the lung CD8+ T cell immune system and analyse if differences exist between *healthy* smokers and COPD patients. If so, these data will help to clarify the (immuno)pathogenesis of COPD. Specifically, we will analyze (1) if the long T cells are maintained through homeostatic control mechanisms distinct from the circulating pool (replicative history measurements), (2) if within the lung selection of particular T cell clones occurs (spectratyping) and (3) the transcriptosome of lung T cells (DNA microarrays). Where possible we will use HLA/*2-microglobuline/viral peptide tetramers to perform the analyses on established virus specific T cells.
A major limitation in current research is the lack of longitudinal studies in smokers at risk to evaluate changes in the local T cell compartment. As a first step we aim to compare BAL from and tissue isolated T cells. In case BAL derived T cells would appear to be representative of tissue residing T cells, BAL T lymphocytes may be used to monitor changes in the local T cell compartment in longitudinal studies.
Understanding the mechanisms that drive the homing and functional differentiation of CD8+ T-cells in the lungs in COPD helps to understand their involvement in its pathogenesis. Insight into the molecular mechanisms may give guidance to develop specific interventions to rebalance this process. This may

ultimately lead to specific interventions that can stop or slow the progression in COPD

Study design

observational study

Study burden and risks

There is no real risk and only a minimaal burden for the lung transplantation patients: only that related to a venapuncture or of taking some extra blood during a regular sampling of blood.

For the lobectomy patients there is a minimal burden related to a venapuncture or of taking some extra blood during a regular sampling of blood.
The sputuminduction may give a light, generally shortlasting sensation of dysnea in patients with COPD.
The risks for the lobectomy patients are minimal related to the sputuminduction, provided that the right precautions are taken and the patients are closely observed. The same holds for the BAL procedure in patients intubated and during the regular monitoring during general anesthesia.

For (ex-)smokers with established COPD there is a potential group benefit in that the findings of the study may lead to new insights into the pathogenesis of COPD and possible new therapies.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

patients scheduled for lobectomy for a small peripheral lung lesion or scheduled lung transplantation

Exclusion criteria

- recent (< 2 weeks) airway infection
- for lung carcinoma patients: use of systemic corticosteroids < 4 weeks before scheduled operation

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-08-2007
Enrollment:	55
Type:	Anticipated

Ethics review

Approved WMO

Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL18422.018.07